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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,812	JAYASHEELA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,8,11,12,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,8,11,12,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/21/2009 has been entered.

Receipt is acknowledged of an amendment, filed 12/21/2009, in which claims 7 and 12 were amended. Claims 7, 8, 11, 12, 22 and 23 are pending.

Election/Restrictions

Applicant elected Group IV with traverse in the reply filed on 7/11/2008. Claims 7, 8, 11, 12, 22 and 23 are under consideration.

Specification

The disclosure is objected to because of the following informalities:

1. Page 9 contains the heading "BRIEF DESCRIPTION OF THE DRAWINGS"; however, the application does not contain any drawings.

2. The citation at page 16, line 12 is incomplete. The "xxxx" should be replaced with the page number.

Appropriate correction is required.

The use of the trademark PROVENTIL (paragraph [0133]) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification does not provide antecedent basis for the term "anti-inflammatory agent" as recited in claim 12.

Response to Arguments - Specification

Applicant's arguments filed 12/21/2009 have been fully considered but they are not persuasive.

The response asserts that the specification was amended to correct the abovementioned informalities; however, the amendment filed 12/21/2009 is non-compliant and has not been entered. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. See 37 CFR 1.121(b)(ii). Furthermore, a proper amendment to paragraph [0078] was received on 5/15/2009. Thus, the changes shown in the amendment filed 12/21/2009 for paragraph [0078] are not necessary and are not relative to the immediate prior version of the paragraph.

Response to Arguments – Claim Objections

The objection of claim 7 has been withdrawn in view of Applicant's amendment to the claim in the reply filed 12/21/2009.

Response to Arguments - 35 USC § 103

Applicant's arguments, see pages 7-11, filed 12/21/2009, with respect to the rejection of claims 7, 8, 11, 12, 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Shinomiya et al (Journal of Virology, Vol. 32, No. 3, pages 958-967, December 1979) in view of Haas et al (The Journal of Infectious Diseases, Vol. 129, No. 4, pages 470-472, April 1974) have been fully considered and are persuasive.

The response states that the art teaches that pyocins are not effective for treating an existing bacterial infection *in vivo*. This statement is supported by the teachings of Haas et al, which show that pyocin is only effective when administered prior to infection (e.g., Table 1). Pyocin has no effect on mortality when administered to mice subsequent to bacterial challenge (e.g., page 470, right column, 4th full paragraph; Table 1). As noted by Applicant, pyocin is shown to be ineffective for treatment of an existing bacterial infection (page 9 of the reply). Furthermore, the response indicates that killing by phage tail proteins is much less efficient than pyocins (Shinomiya et al. page 966, left column, last full paragraph). Given the inability of pyocin to treat an existing infection in mice, it would have been unpredictable to use a phage tail to treat an existing infection.

The previous rejection of claims 7, 8, 11, 12, 22 and 23 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 8, 11, 12, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 7 is drawn to a method of reducing a bacterial population in a subject in need of treatment. The method comprises the step of administering a therapeutically effective amount of a composition comprising an isolated phage tail that inhibits the growth of a target bacterium, thereby reducing the growth of the bacterial population. The specification teaches that "growth inhibition" encompasses slowing the rate of bacterial cell division, stopping bacterial cell division, or killing the bacteria (e.g., paragraph [0048]). Claim 8 depends from claim 7 and requires that (i) said subject is a human; (ii) said subject is a primate, a

food, work, display or companion animal; (iii) said target bacterium is *Escherichia, Staphylococcus, Pseudomonoas,* or *Streptococcus*; (iv) said method further comprises administering a second therapeutic or antimicrobial agent, including administering systemically, parenterally, orally, topically, or by inhalation, catheter, or drain tube; (v) said method results in a relative decrease in said population of at least 10-1000 fold; **or** (vi) said method results in a decrease in detectability of said population by at least 5-50 fold. The nature of the invention is complex in that the administration of the phage tail must inhibit the growth of a target bacterium, thereby reducing the growth of the bacterial population, including the specific bacterial populations and levels of reduction recited in claim 8.

Claim 11 is drawn to a method of treating a bacterial infection in a subject in need of such treatment. The method comprises the step of administering a therapeutically effective amount of a pharmaceutical composition comprising an isolated phage tail, wherein said isolated phage tail inhibits the growth of a target bacterium, thereby treating the bacterial infection. Claim 12 depends from claim 11 and requires that (i) said subject is a human; (ii) said subject is a primate, a food, work, display or companion animal; (iii) said pharmaceutical composition is administered systemically, parenterally, orally, topically, or by inhalation, catheter, or drain tube; **or** (iv) said pharmaceutical composition is administered in combination with a second therapeutic selected from the group consisting of an anti-bacterial agent, an anti-microbial, inflammatory, and anti-inflammatory agent. The nature of the invention is complex in that the administration of the phage tail must inhibit the growth of a target bacterium, thereby reducing the growth of the bacterial population and treating the existing infection. Furthermore, the

invention is complex in that both an inflammatory agent and an anti-inflammatory agent must be capable of treating a bacterial infection.

Claim 22 is drawn to a method of treating a bacterial colonization in a eukaryote experiencing colonization by a target bacterium. The method comprises the step of administering to the eukaryote a defined dose therapeutic anti-bacterial composition comprising an isolated phage tail, thereby treating the bacterial colonization. Claim 23 depends from claim 22 and requires that (i) said eukaryote is a mammal, including a primate; (ii) said eukaryote is a food, work, display or companion animal; (iii) said target bacterium is a pathogenic, nosocomial, or pyogenic bacterium; said target bacterium is an *Escherichia, Staphylococcus, Pseudomonas,* or *Streptococcus* bacterium; (iv) said composition is administered systemically, parenterally, orally, topically, or by inhalation, catheter, or drain tube; (v) said colonization has already been treated with an anti-microbial antibiotic; (vi) said colonization has been diagnosed to be susceptible to the selected composition; **or** (vii) said eukaryote is also inoculated with another bacterium to replace said target bacterium. The nature of the invention is complex in that the administration of the phage tail must inhibit the growth of a target bacterium, thereby reducing the growth of the bacterial population and treating the existing infection.

Breadth of the claims: The claims are broadly drawn to the administration of any isolated phage tail from any phage. Further, the claims are broadly drawn to reducing the growth and treating the infection of any bacterial species. Moreover, the claims are drawn to treating an infection in any subject. The specification defines "subject in need of treatment" as an animal or plant with a bacterial infection that is potentially life-threatening or that impairs health or

shortens the lifespan of the animal (e.g., paragraph [0059]). The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches that a tailed bacteriophage generally comprises a head, called the capsid, and a tail (e.g., paragraph [0007]). The tail structure has a tube, a sheath covering the tube, tail fibers and a base plate, where each of the structures is made of or contains different proteins (e.g., paragraph [0113]). The specification teaches that phage tail and phage tail-like structures can be similarly described as bacteriophage structures that are essentially devoid of phage DNA (and phage replication) while retaining killing function (e.g., paragraph [0007]). Further, the specification teaches that pyocins are "believed to be tail-like portions of tailed phages" (paragraph [0008]). The specification provides general methods for the production of phage tail (e.g., paragraphs [0157]-[0158]).

The specification envisions treating a bacterial infection in a subject by administering an anti-bacterial phage fragment, such as a phage tail (e.g., paragraphs [0021] and [0045]). The specification envisions using the tailed portion of a phage from the Siphoviridae or Myoviridae families (e.g., paragraph [0042]) to treat infections of gram negative or gram positive bacteria (e.g., paragraph [0095]). The specification envisions determining by an *in vitro* assay the "killing units" of the composition to be administered to the subject and formulating the composition for delivery by an intravenous, intramuscular, intraperitoneal, intrathecal, vaginal, rectal, topical, lumbar puncture, direct application to the brain and/or meninges, etc. (e.g., paragraphs [0130]-[0143]).

The specification does not contain any working examples of the claimed invention. The working examples are limited to testing the *in vitro* activity of the P9042 and P954 phage tails. The specification teaches that P9042 and P954 are examples of phages that were isolated from nature and are capable of being propagated in *Staphylococcus aureus* (e.g., paragraph [0163]). P9042 is a lytic phage, and P954 is a lysogenic phage (e.g., paragraph [0163]). In Example 2, the killing activity of P9042 tails was determined using *Staphylococcus simulans* as the target. The P9042 phage tails were capable of killing *Staphylococcus simulans* (e.g., paragraph [0170]). In Example 3, the killing activity of P954 tails was determined using *S. aureus* B935 as the target. The phage tails were able to kill *S. aureus* B935 (e.g., paragraph [0183]). Further, the specification teaches that *S. aureus* strains B935, B904, B913, B920, B903, B975, and B972 each harbor receptors for attachment of phage P954 (e.g., paragraph [0184]). These strains were tested for P954 phage tail-based killing and each was susceptible (e.g., paragraph [0188]). The ability of the P954 phage tail to kill *S. aureus* B935 was confirmed in Example 4. Under the disclosed *in vitro* assay conditions, tail killing activity started as early as 10 min, whereas the doubling time of the bacteria was about 25 min (e.g., paragraph [0194]). Furthermore, the P954 tail preparations were tested against 33 clinical isolates of *Staphylococcus aureus* collected from hospitals in Bangalore, India (e.g., paragraph [0200]). The tail preparation was capable of killing >80% isolates, whereas the whole phage was capable of killing only about 12% of the isolates (e.g., paragraph [0201]). Example 5 demonstrates that the P9042 tails were not inactivated with trypsin but were unstable after heat treatment, whereas P954 tails were sensitive to trypsin (e.g., paragraph [0205]). No working examples are provided where phage tail killing activity was determined *in vivo*. Phage tails were not administered to subjects or eukaryotes infected with

bacteria. In summary, the specification provides evidence that the P954 and P9042 phage tails are capable of killing *Staphylococcus simulans* and *Staphylococcus aureus in vitro*.

The description of the specification does not provide support for the administration of an anti-inflammatory agent to reduce bacterial growth or treat a bacterial infection.

Predictability and state of the art: It would have been unpredictable to extrapolate the *in vitro* bacterial killing activity of phage tail preparations to the treatment of bacterial infections in subjects *in vivo*. While the prior art does not specifically test the correlation between *in vitro* and *in vivo* activity of phage tails *per se*, the prior art does assess the ability of pyocins, which are phage tail-like preparations (e.g., specification at paragraph [0008]). Furthermore, the prior art has considered the *in vitro* killing activity of phage tail to be similar to that of R-type pyocins (Shinomiya et al. Journal of Virology, Vol. 32, No. 3, pages 958-967, December 1979, cited in a prior action; e.g., page 966, left column).

Merrikin et al (Applied Microbiology, Vol. 23, No. 1, pages 164-165, January 1972) teach that pyocin 78-C2 is not effective in treating existing *Pseudomonas aeruginosa* infection in mice. Pyocin was effective against strain 320 when administered intravenously immediately after infection or intravenously 6 hours after infection (e.g., page 164, paragraph bridging columns, and right column, 2nd full paragraph). Pyocin was effective against strain 325 when administered intravenously immediately after infection (e.g., page 164, paragraph bridging columns, and right column, 2nd full paragraph). However, pyocin was not effective against either of these strains when administered intravenously 24 hours after infection (e.g., page 164, paragraph bridging columns, and right column, 2nd full paragraph). Moreover, pyocin was not effective in any administration schedule against strain 327 even though the strain is sensitive to

pyocin *in vitro* (e.g., page 164, right column, 2nd full paragraph). Thus, Merrikin et al teach that the effectiveness of pyocin *in vitro* does not always correlate to the effectiveness *in vivo*, and for the pyocin to be effective *in vivo* it must be administered within 6 hours of infection.

Similarly, Haas et al (The Journal of Infectious Diseases, Vol. 129, No. 4, pages 470-472, April 1974, cited in a prior action) teaches that a pyocin with lytic activity *in vitro* against sensitive strains at dilutions of 1:1,000 had no effect on the mortality of mice infected with a sensitive *P. aeruginosa* strain when the pyocin was administered after bacterial infection of the mouse (e.g., page 470, right column; Table 1).

Williams (Journal of Medical Microbiology, Vol. 9, pages 153-161, 1976) teaches the production of pyocins from *P. aeruginosa* strains 1577, 5882 and H108, which were described as contractile, filamentous, and small, respectively (e.g., page 154, *Selection of pyogenic strains*). Each of the pyocins had activity against *P. aeruginosa* strain P14 *in vitro* (e.g., page 154, 3rd full paragraph). Williams teaches that mice that received bacteria before the injection of pyocin died (pyocin administered 3 or 6 hr after bacteria), whereas mice that received pyocin before or along with the bacteria had a considerably lower mortality (e.g., page 157, last paragraph; Table III; page 159, 3rd full paragraph). Further, Williams teaches that pyocin administration to burned mice did not reduce the growth of *P. aeruginosa* on the burn (e.g., page 158, 3rd and 4th paragraphs). Williams concludes that the outlook for pyocin therapy is not favorable (e.g., page 160, 4th paragraph).

In sum, the prior art teaches that pyocins are not effective for reducing bacterial growth and treating an existing bacterial infection *in vivo*. Further, phage tails kill by a single-hit process but are less effective at killing *in vitro* as compared to pyocins (Shinomiya et al. page

966, left column, last full paragraph). Thus, one would not have an expectation of success in extrapolating results from *in vitro* killing assays to *in vivo* methods of reducing bacterial growth and treating bacterial infections by administering an isolated phage tail.

The post-filing art teaches that the *in vivo* susceptibility of bacteria to bacteriophages is still largely poorly understood, and further research on phage-bacterium systems must be undertaken to define the requirements for successful phage treatments (Skurnik et al. International Journal of Medical Microbiology, Vol. 296, pages 5-14, February 2006; e.g., Abstract; page 11, Conclusions). Further, Skurnik et al teach that the use of phage tail-like bacteriocins (pyocins) as antimicrobial agents most likely will be limited only to *in vitro* applications (e.g., paragraph bridging pages 8-9). The tail-like structures are only effective when administered immediately after infection (Skurnik et al. paragraph bridging pages 8-9; Merrikin et al. page 164, paragraph bridging columns, and right column, 2nd full paragraph; Haas et al. page 470, right column; Table 1). Thus, the phage tail is likely only to be effective in experimental models where the phage tail is administered prior to a known time point of infection or at the same time as experimentally induced infection. It would be unpredictable to use phage tail to reduce bacterial growth in an existing infection in a eukaryotic organism.

Amount of experimentation necessary: In view of the unpredictable nature of the invention, the quantity of experimentation would be large. One would be required to test each phage tail from a particular phage for the ability to reduce bacterial growth of a specific bacterial species and strain *in vivo*. The effectiveness of one phage tail with one particular strain *in vivo* would not provide any estimation of effectiveness of the same phage tail against another strain or a different phage tail against the same strain.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 7, 8, 11, 12, 22 and 23 are not considered to be enabled by the instant specification.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 8, 11, 12, 22 and 23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8-16 and 19-24 of copending Application No. 11/915,272. This is a new rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to administering a phage tail to reduce a bacterial population in an animal.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636